



ATGGCCCAAGCCCTGCCCTGGCTCCTGCTGTGGATGGGCGCGGGAGT
GCTGCCTGCCCACGGCACCCAGCACGGCATCCGGCTGCCCCTGCGCA
GCGGCCTGGGGGGCGCCCCCTGGGGCTGCGGCTGCCCCGGGAGAC
CGACGAAGAGCCCCGAGGAGCCCCGGCCGGAGGGGCAGCTTTGTGGAGA
TGGTGGACAACCTGAGGGGGCAAGTCGGGGGCAGGGCTACTACGTGGAG
ATGACCGTGGGCAGCCCCCGCAGACGCTCAACATCCTGGTGGATACA
GGCAGCAGTAACTTTGCAGTGGGTGCTGCCCCCACCCTTCCTGCAT
CGCTACTACCAGAGGCAGCTGTCCAGCACATAACGGGACCTCCGGAAG
GGTGTGTATGTGCCCTACACCCAGGGCAAGTGGGAAGGGGAGCTGGG
CACCGACCTGGTAAGCATCCCCCATGGCCCCAACGTCACTGTGCGTGC
CAACATTGCTGCCATCACTGAATCAGACAAGTTCTTCATCAACGGCTCC
AACTGGGAAGGCATCCTGGGGCTGGCCTATGCTGAGATTGCCAGGCCT
GACGACTCCCTGGAGCCTTTCTTTGACTCTCTGGTAAAGCAGACCCACG
TTCCCAACCTCTTCTCCCTGCAGCTTTGTGGTGCTGGCTTCCCCCTCAA
CCAGTCTGAAGTGCTGGCCTCTGTCTGGAGGGAGCATGATCATTGGAGG
TATCGACCACTCGCTGTACACAGGCAGTCTCTGGTATACACCCATCCGG
CGGGAGTGGTATTATGAGGTGATCATTGTGCGGGTGGAGATCAATGGA
CAGGATCTGAAAATGGACTGCAAGGAGTACAACCTATGACAAGAGCATTG
TGGACAGTGGCACCAACCAACCTTCGTTTGCCCAAGAAAGTGTTTGAAGC
TGCAGTCAAATCCATCAAGGCAGCCTCCTCCACGGAGAAGTTCCCTGAT
GGTTTCTGGCTAGGAGAGCAGCTGGTGTGCTGGCAAGCAGGCACCACC
CCTTGGAACATTTTCCCAGTCATCTCACTCTACCTAATGGGTGAGGTTAC
CAACCAGTCCTTCCGCATCACCATCCTTCCGCAGCAATACCTGCGGCCA
GTGGAAGATGTGGCCACGTCCCAAGACGACTGTTACAAGTTTGCCATCT
CACAGTCATCCACGGGCACTGTTATGGGAGCTGTTATCATGGAGGGCTT
CTACGTTGTCTTTGATCGGGCCCCGAAACGAATTGGCTTTGCTGTCAGC
GCTTGCCATGTGCACGATGAGTTCAGGACGGCAGCGGTGGAAGGCCCT
TTTGTACCTTGGACATGGAAGACTGTGGCTACAACATTCCACAGACAG
ATGAGTCAACCCTCATGACCATAGCCTATGTCATGGCTGCCATCTGCGC
CCTCTTCATGCTGCCACTCTGCCTCATGGTGTGTCAGTGGCGCTGCCTC
CGCTGCCTGCGCCAGCAGCATGATGACTTTGCTGATGACATCTCCCTGC
TGAAG

FIG. 1A

CCATGCCGGCCCCCTCACAGCCCCGCCGGGAGCCCCGAGCCCCGCTGCCCAGGCTGGC
CGCCGCSGTGCCGATGTAGCGGGCTCCGGATCCCAGCCTCTCCCCTGCTCCCGTGC
TCTGCGGATCTCCCCTGACCGCTCTCCACAGCCCCGGACCCGGGGGCTGGCCCAGG
GCCCTGCAGGCCCTGGCGTCCTGATGCCCCCAAGCTCCCTCTCCTGAGAAGCCACC
AGCACCAACCAGACTTGGGGGCGAGGCGCCAGGGACGGACGTGGGCCAGTGCAGAGC
CCAGAGGGCCCCGAAGGCCGGGGCCCCACCATGGCCCCAAGCCCTGCCCTGGCTCCTG
CTGTGGATGGGCGCGGGAGTGCTGCCTGCCCCACGGCACCCAGCACGGCATCCGGC
TGCCCCCTGCGCAGCGGCCTGGGGGGCGCCCCCCTGGGGCTGCGGCTGCCCCGGG
AGACCGACGAAGAGCCCCGAGGAGCCCCGGCCGGAGGGGCAGCTTTGTGGAGATGGT
GGACAACCTGAGGGGCAAGTCGGGGCAGGGGCTACTACGTGGAGATGACCGTGGGC
AGCCCCCGCAGACGCTCAACATCCTGGTGGATACAGGCAGCAGTAACCTTTCAGT
GGGTGCTGCCCCCACCCTTCCTGCATCGCTACTACCAGAGGCAGCTGTCCAGCA
CATACCGGGACCTCCGGAAGGGTGTGTATGTGCCCTACACCCAGGGCAAGTGGGAA
GGGGAGCTGGGCACCGACCTGGTAAGCATCCCCCATGGCCCCAACGTCACTGTGCG
TGCCAACATTGCTGCCATCACTGAATCAGACAAGTTCTTCATCAACGGCTCCAAGTGG
GAAGGCATCCTGGGGCTGGCCTATGCTGAGATTGCCAGGCCTGACGACTCCCTGGA
GCCTTTCTTTGACTCTCTGGTAAAGCAGACCCACGTTCCCAACCTCTTCTCCCTGCAG
CTTTGTGGTGGCTTCCCCCTCAACCAGTCTGAAGTGCTGGCCTCTGTGCGGAGG
GAGCATGATCATTGGAGGTATCGACCACTCGCTGTACACAGGCAGTCTCTGGTATAC
ACCCATCCGGCGGGAGTGGTATTATGAGGTGATCATTGTGCGGGTGGAGATCAATG
GACAGGATCTGAAAATGGACTGCAAGGAGTACAACCTATGACAAGAGCATTGTGGACA
GTGGCACCACCAACCTTCGTTTGCCCAAGAAAGTGTTTGAAGCTGCAGTCAAATCCA
TCAAGGCAGCCTCCTCCACGGAGAAGTTCCCTGATGGTTTCTGGCTAGGAGAGCAG
CTGGTGTGCTGGCAAGCAGGCACCAACCCCTTGGAACATTTTCCAGTCATCTCACTC
TACCTAATGGGTGAGGTTACCAACCAGTCCTTCCGCATCACCATCCTTCCGCAGCAA
TACCTGCGGCCAGTGGAAGATGTGGCCACGTCCCAAGACGACTGTTACAAGTTTGCC
ATCTCACAGTCATCCACGGGCACTGTTATGGGAGCTGTTATCATGGAGGGCTTCTAC
GTTGTCTTTGATCGGGCCCCGAAAACGAATTGGCTTTGCTGTCAGCGCTTGCCATGTG
CACGATGAGTTCAGGACGGCAGCGGTGGAAGGCCCTTTTGTACCTTGACATGGA
AGACTGTGGCTACAACATTCCACAGACAGATGAGTCAACCCTCATGACCATAGCCTA
TGTATGGCTGCCATCTGCGCCCTCTTCATGCTGCCACTCTGCCTCATGGTGTGTCA
GTGGCGCTGCCTCCGCTGCCTGCGCCAGCAGCATGATGACTTTGCTGATGACATCT
CCCTGCTGAAGTGAGGAGGCCCATGGGCAGAAGATAGAGATTCCCCTGGACCACAC
CTCCGTGGTTCACTTTGGTCACAAGTAGGAGACACAGATGGCACCTGTGGCCAGAG
CACCTCAGGACCCTCCCCACCCACCAAATGCCTCTGCCTTGATGGAGAAGGAAAAG
GCTGGCAAGGTGGGTTCCAGGGACTGTACCTGTAGGAAACAGAAAAGAGAAGAAAAG
AAGCACTCTGCTGGCGGGAATACTCTTGGTCACCTCAAATTTAAGTCGGGAAATTCT
GCTGCTTGAACTTCAGCCCTGAACCTTTGTCCACCATTCTTTAAATTCTCCAACCC
AAAGTATTCTTCTTTTCTTAGTTTCAGAAAGTACTGGCATCACACGCAGGTTACCTTGG
CGTGTGTCCCTGTGGTACCCTGGCAGAGAAGAGACCAAGCTTGTTTCCCTGCTGGC
CAAAGTCAGTAGGAGAGGATGCACAGTTTGCTATTTGCTTTAGAGACAGGGACTGTA
TAAACAAGCCTAACATTGGTGCAAAGATTGCCTCTTGAATT

FIG. 1B

MAQALPWLLLWMGAGVLP AHGTQH GIRLPLRSGLG GAPLGLRLP
RETDEEPEEPGRRGSFVEMVDNLRGKSGQGYYVEMTVGSPPQT
LNILVDTGSSNFAVGAAPHPFLHRYYQRQLSSTYRDLRKGVYVPY
TQGKWE GELGTDLVSIPHGPNVTVRANIAAITESDKFFINGSNWE
GILGLAYAEIARPDDSLEPFFDSL VKQTHVPNLFSLQLCGAGFPLN
QSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVIIVRVEIN
GQDLKMDCKEYNYDKSIVDSGTTNLRLPKKVFEAAVKSIIKAASST
EKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTNQSFRIT
ILPQQYL RPVEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYV
FDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMEDCGYNIPQ
TDESTLMTIAYVMAAICALFMLPLCLMVCQWRCLRCLRQQHDDF
ADDISLLK

FIG. 2A

ETDEEPEEPGRRGSFVEMVDNLRGKSGQGYYVEMTVGSPPQT
LNILVDTGSSNFAVGAAPHPFLHRYYQRQLSSTYRDLRKGVYVPY
TQGKWEDELGTDLVSIPHGPNVTVRANIAAITESDKFFINGSNWE
GILGLAYAEIARPDDSLEPFFDSL VKQTHVPNLFSLQLCGAGFPLN
QSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVIIVRVEIN
GQDLKMDCKEYNYDKSIVDSGTTNLRLPKKVFEAAVKSIIKAASST
EKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTNQSFRIT
ILPQQYL RPVEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVV
FDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMEDCGYNIPQ
TDESTLMTIAYVMAAICALFMLPLCLMVCQWRCLRCLRQQHDDF
ADDISLLK

FIG. 2B

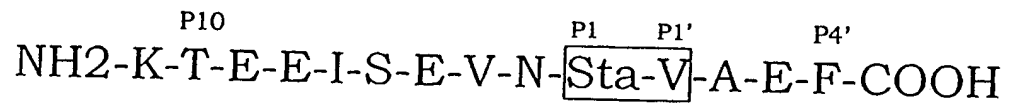
FIG. 3A

MAQALPWLLLWMGAGVLPÄHGTQHGI RLPLRSGLGGAPLGLRLPRETDEEPE
EPGRRGSFVEMVDNLRGKSGQGYVEMT
VGSP PQTLN ILVDTGSSNFAVGAAPHPFLHRYYQRQLSSTYRDLRKGVVVPYT
QGKWE GELGTDLV SIPHGPNVTVRANI
AAITESDKFFINGSNWE GILGLAYAEIARPDDSLEPFFDSL VKQTHVPNL FSLQL
CGAGFPLNQSEVLASVGGSMIIGGI
DHSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKEYNYDKSIVDSGTTNL
RLPKKVFEAAVKS IKAASSTEKFPD
GFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTNQSFRTILPQQYL RPVEDVA
TSQDDCYKFAISQSSTGTVMGAVIME
GFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMEDCGYNIPQTDED
YKDDDDK

FIG. 3B

ETDEEPEEPGRRGSFVEMVDNLRGKSGQGYVEMT
VGSP PQTLN ILVDTGSSNFAVGAAPHPFLHRYYQRQLSSTYRDLRKGVVVPYT
QGKWE GELGTDLV SIPHGPNVTVRANI
AAITESDKFFINGSNWE GILGLAYAEIARPDDSLEPFFDSL VKQTHVPNL FSLQL
CGAGFPLNQSEVLASVGGSMIIGGI
DHSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKEYNYDKSIVDSGTTNL
RLPKKVFEAAVKS IKAASSTEKFPD
GFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTNQSFRTILPQQYL RPVEDVA
TSQDDCYKFAISQSSTGTVMGAVIME
GFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMEDCGYNIPQTDED
YKDDDDK

FIG. 4



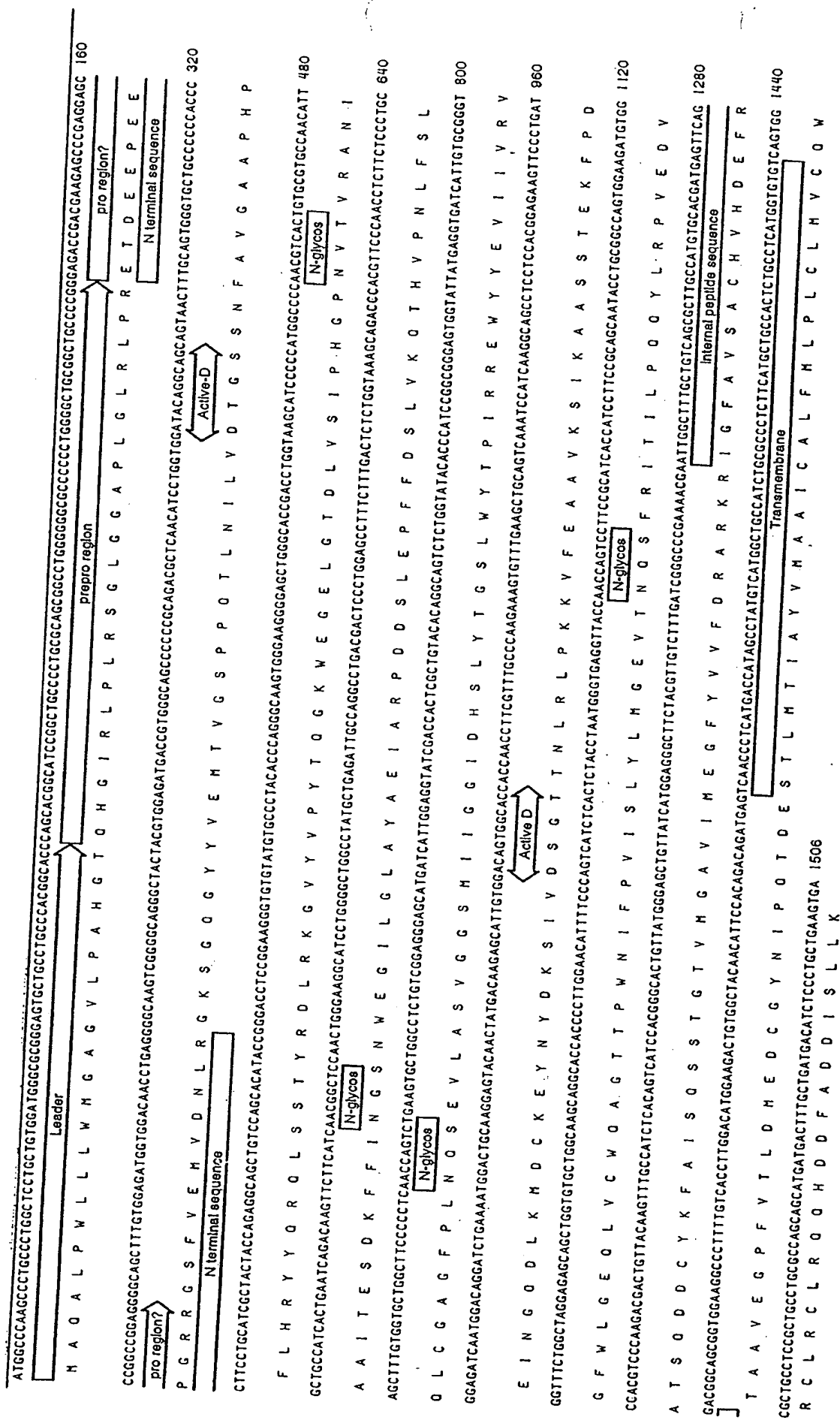


FIG. 5

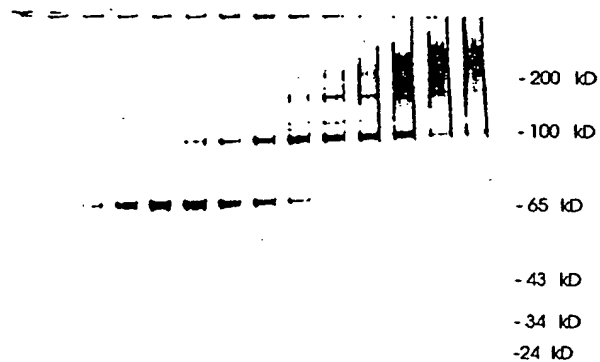
load
Flow thru
fraction
11 12 13 14 15 16 17 18 19 20 21 22



REDUCING (+ β ME)

FIG. 6A

fraction
11 12 13 14 15 16 17 18 19 20 21 22 23 24



NONREDUCING (NO β ME)

FIG. 6B

FIG. 7

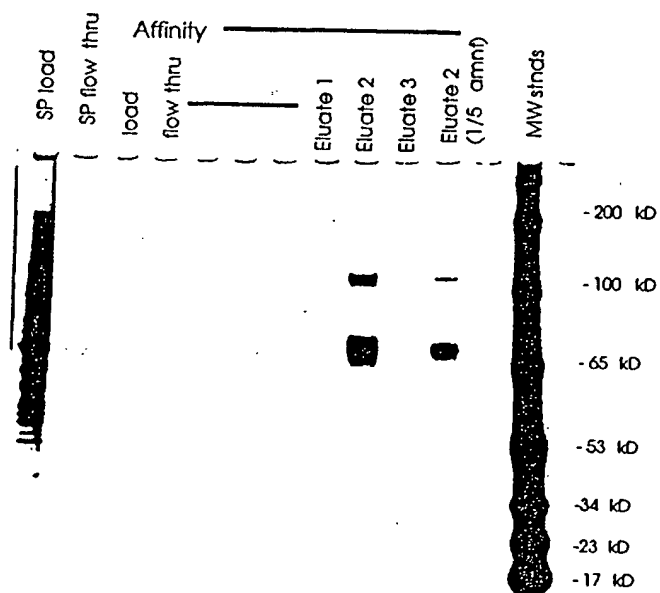
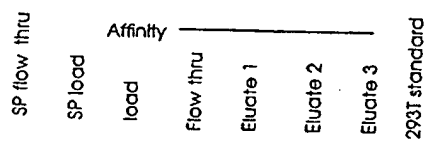


FIG. 8



E T D E E P E E P G R R G S F V E M V D N
 GARACNGAYGARGARCCNGARGARCCNGGNHGNHGNHGNHGNWSNTTYGTNGARATGGTNGAYAAY 63

3427-3430
 5' primer set 1

3431-3434
 3' primer set 1

3448-3451
 5' primer set 2

3452-3455
 3' primer set 2

1⁰ HNC/primer set 1

(3428+3433)
 54 bp product

1⁰HNC & IMR32/ primer set 2

72 bp product

sequence:

set2 3460
 5' RACE primer
 CCCGAAGAGCCCGGCCGGAGGGGCAGCTTTGTCCA 35
 P E E P G R R G S F V
 ORF
 3'RACE primer 3459
 set 2

FIG. 9

Concentration dependence of β -secretase P1' mutant peptides

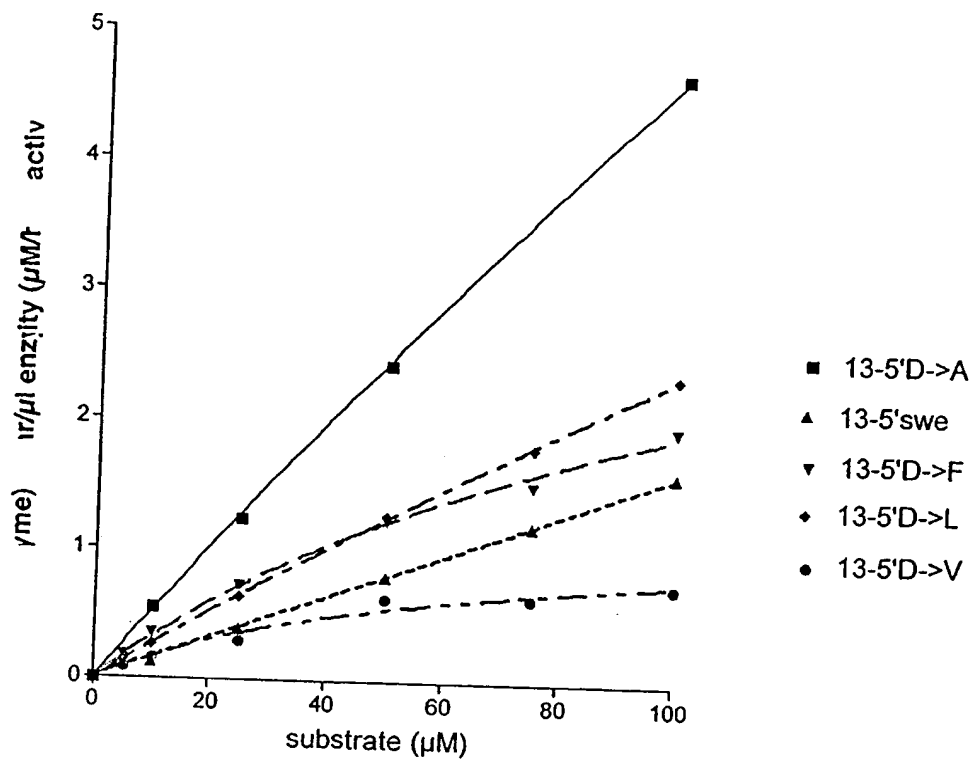


FIG. 11

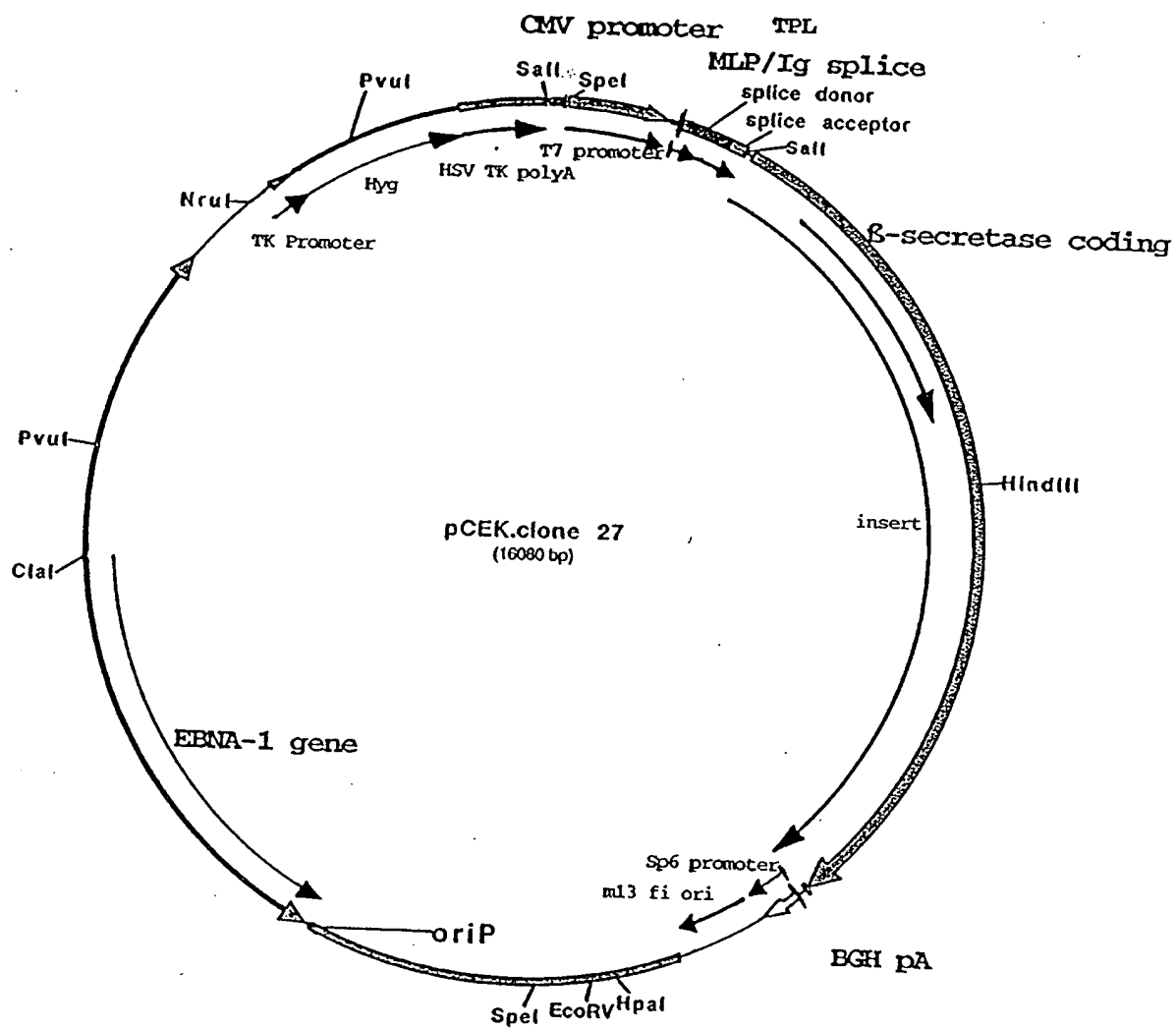


FIG. 12

FIG. 13A

1 TTCTCATGTTTGACAOCTTATCATOGCAGATCOGGGCAAGTGTGCTATGCTGCAGGCGCAGAACTGGTAGGTATGGAAGATCOGATGTACGGGCCAGATATAC
SpeI
107 OCGTTGACATTGATTATTGACTAGTTATTAATAGTAATCAATTAAGGGGTCATTAGTTCATAGCCATATATGGAGTTGCGGTTACATAACTTAACGTAAATGGC
213 COGCTGGCTGACCGCCCAAGACCCCGGCCATTGACGTCAATAATGACGTATGTTCCATAGTAACGCCAATAGGGACTTTCCATTGAAGTCAATGGGTGGACT
319 ATTTAAGGTAACTGCGCACTTGGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGAAGTCAATGAAGTAAATGGCCCGCTGGCATTATGCCCA
425 GTACATGAOCTTATGGGACTTTCTACTTGGCAGTACATCTACGTATTAGTCATOGCTATTACCATGGTGATGCGGTTTGGCAGTACATCAATGGGCGTGATAG
531 CGGTTTGACTCAOCCGGGATTTTCAAGTCTCCACCCCATTTGACGTCAATGGGAGTTTGTGTTGGCACCAAAATCAACGGGACTTTCCAAAATGTGTAACTAACC
637 CCCCATTGAAGCAAATGGCGGTAGCGGTGTACGGTGGGAGGTCTATATAAGCAGAGCTCTCTGGCTAACTAGAGAAACCACTGCTTACTGGCTTATCGAAATTAA
743 TAAGACTCACTATAGGAGAACCAAGCTCTGTGGGCTGGCGGTGAGGACAACTCTTGGCGGTCTTTTCAGTACTCTTGGATCGGAAACCGTGGCGCTCGAA
849 OGGTACTCGGCCACGAGGGAOCTGAGOGAGTCCGCATGACCGGATGGGAAAACCTCTOGACTGTTGGGGTGAGTACTCCCTCTCAAAAGGGGCATGACTTCTG
splice donor
955 CGCTAAGATTGTGAGTTTCCAAAAACGAGGAGGATTTGATATTCACCTGGCCCGGGGTGATGCTTTGAGGGTGGCGCGTCCATCTGGTCAGAAAAGACAATCTT
1061 TTGTGTCAAGCTTGAGGTGTGGCAGGCTTGAGATCTGGOCATACACTTGAGTGACAATGACATCCACTTTGCTTTCTCTCCACAGGTGTCCACTCCCGAGTCC
splice acceptor
SalI
1167 AACTGAGGTGACTCTAGACCCGGGAATTCTGTCAGATATCCATCACTGGCGCACTGCTCCCGAGCCCGCGGGGAGCTGGAGCCCGAGCTGGATTATGG
1273 TGGCTGAGCAGCCAAAGCAGCCGAGGAGCCCGGAGCCCTTGGCCCTGCCCCGCGCGCGCGCGCGCGGGGGAACAGGGAAGCCGCCACCGCCCGCCATGCCCC
1379 CCCCCTCCAGCCCCCGCGGAGCCCCGCGCGCGCTGCCCCAGGCTGGCCGCGCGCGTGGCGATGTAGCGGGCTCCCGATCCAGGCTCTCCCCCTGCTCCCGTCTCTG
1485 CGGATCTCCCTGACCGCTCTCCACAGCCCGGAGCCCGGGGCTGGCCAGGGGCTGCGAGGCGCTGGGCTCTGATGCCCCCAAGCTCCCTCTCTGAGAAGCCAC
1591 CAGCACCAACAGACTTGGGGGCGAGGCCAGGAGCGGACGTGGGCGAGTGGAGGCCAGAGGGCCCGAAGGCGGGGCCCAAC ATG GGC CAA GGC CTG
1 Met Ala Gln Ala Leu
1690 CCC TGG CTC CTG CTG TGG ATG GGC GGC GGA GTG CTG OCT GGC CAC GGC ACC CAG CAC GGC ATC CCG CTG CCC CTG GGC
6 Pro Trp Leu Leu Leu Trp Met Gly Ala Gly Val Leu Pro Ala His Gly Thr Gln His Gly Ile Arg Leu Pro Leu Arg
1768 AGC GGC CTG GGC GGC GGC CCC CTG GGC CTG GGC CTG CCC CCG GAG ACC GAC GAA GAG CCC GAG GAG CCC GGC CCG AGG
32 Ser Gly Leu Gly Gly Ala Pro Leu Gly Leu Arg Leu Pro Arg Glu Thr Asp Glu Glu Pro Glu Glu Pro Gly Arg Arg
1846 GGC ACC TTT GTG GAG ATG GTG GAC AAC CTG AGG GGC AAG TGG GGC CAG GGC TAC TAC GTG GAG ATG ACC GTG GGC AGC
58 Gly Ser Phe Val Glu Met Val Asp Asn Leu Arg Gly Lys Ser Gly Gln Gly Tyr Tyr Val Glu Met Thr Val Gly Ser
1924 CCC CCG CAG ACG CTC AAC ATC CTG GTG GAT ACA GGC ACC AGT AAC TTT GCA GTG GGT GCT GGC CCC CAC CCC TTC CTG
84 Pro Pro Gln Thr Leu Asn Ile Leu Val Asp Thr Gly Ser Ser Asn Phe Ala Val Gly Ala Ala Pro His Pro Phe Leu
2002 CAT CCG TAC TAC CAG AGG CAG CTG TCC AGC ACA TAC CCG GAC CTC CCG AAG GGT GTG TAT GTG CCC TAC ACC CAG GGC
110 His Arg Tyr Tyr Gln Arg Gln Leu Ser Ser Thr Tyr Arg Asp Leu Arg Lys Gly Val Tyr Val Pro Tyr Thr Gln Gly
2080 AAG TGG GAA GGC GAG CTG GGC ACC GAC CTG GTA AGC ATC CCC CAT GGC CCC AAC GTC ACT GTG GGT GGC AAC ATT GCT
136 Lys Trp Glu Gly Glu Leu Gly Thr Asp Leu Val Ser Ile Pro His Gly Pro Asn Val Thr Val Arg Ala Asn Ile Ala
2158 GGC ATC ACT GAA TCA GAC AAG TTC TTC ATC AAC GGC TCC AAC TGG GAA GGC ATC CTG GGC CTG GGC TAT GCT GAG ATT
162 Ala Ile Thr Glu Ser Asp Lys Phe Phe Ile Asn Gly Ser Asn Trp Glu Gly Ile Leu Gly Leu Ala Tyr Ala Glu Ile
2236 GGC AGG CCT GAC GAC TCC CTG GAG CCT TTC TTT GAC TCT CTG GTA AAG CAG ACC CAC GTT CCC AAC CTC TTC TCC CTG
188 Ala Arg Pro Asp Asp Ser Leu Glu Pro Phe Phe Asp Ser Leu Val Lys Gln Thr His Val Pro Asn Leu Phe Ser Leu
2314 CAG CTT TGT GGT GCT GGC TTC CCC CTC AAC CAG TCT GAA GTG CTG GGC TCT GTC GGA GGC AGC ATG ATC ATT GGA GGT
214 Gln Leu Cys Gly Ala Gly Phe Pro Leu Asn Gln Ser Glu Val Leu Ala Ser Val Gly Gly Ser Met Ile Ile Gly Gly
2392 ATC GAC CAC TGG CTG TAC ACA GGC AGT CTC TGG TAT ACA CCC ATC CCG CCG GAG TGG TAT TAT GAG GTC ATC ATT GTG
240 Ile Asp His Ser Leu Tyr Thr Gly Ser Leu Trp Tyr Thr Pro Ile Arg Arg Glu Trp Tyr Tyr Glu Val Ile Ile Val
2470 CCG GTG GAG ATC AAT GGA CAG GAT CTG AAA ATG GAC TGC AAG GAG TAC AAC TAT GAC AAG AGC ATT GTG GAC AGT GGC
266 Arg Val Glu Ile Asn Gly Gln Asp Leu Lys Met Asp Cys Lys Glu Tyr Asn Tyr Asp Lys Ser Ile Val Asp Ser Gly
2548 ACC ACC AAC CTT CGT TTG CCC AAG AAA GTG TTT GAA GCT GCA GTC AAA TCC ATC AAG GCA CCC TCC TCC ACG GAG AAG
292 Thr Thr Asn Leu Arg Leu Pro Lys Lys Val Phe Glu Ala Ala Val Lys Ser Ile Lys Ala Ala Ser Ser Thr Glu Lys
2626 TTC OCT GAT GGT TTC TGG CTA GGA GAG CAG CTG GTG TCC TGG CAA GCA GGC ACC ACC CCT TGG AAC ATT TTC CCA GTC
318 Phe Pro Asp Gly Phe Trp Leu Gly Glu Gln Leu Val Cys Trp Gln Ala Gly Thr Thr Pro Trp Asn Ile Phe Pro Val

FIG. 13B

2704 ATC TCA CTC TAC CTA ATG GGT GAG GTT ACC AAC CAG TCC TTC GGC ATC ACC ATC CTT CCG CAG CAA TAC CTG CCG CCA
 344 Ile Ser Leu Tyr Leu Met Gly Glu Val Thr Asn Gln Ser Phe Arg Ile Thr Ile Leu Pro Gln Gln Tyr Leu Arg Pro

2782 GTG GAA GAT GTG GGC ACG TCC CAA GAC GAC TGT TAC AAG TTT GGC ATC TCA CAG TCA TCC ACG GGC ACT GTT ATG GGA
 370 Val Glu Asp Val Ala Thr Ser Gln Asp Asp Cys Tyr Lys Phe Ala Ile Ser Gln Ser Ser Thr Gly Thr Val Met Gly

2860 GCT GTT ATC ATG GAG GGC TTC TAC GTT GTC TTT GAT GGC GCA AAA CCA ATT GGC TTT GCT GTC ACG GCT TCC CAT
 396 Ala Val Ile Met Glu Gly Phe Tyr Val Val Phe Asp Arg Ala Arg Lys Arg Ile Gly Phe Ala Val Ser Ala Cys His

2938 GTG CAC GAT GAG TTC AGG ACG GCA GCG GTG GAA GGC OCT TTT GTC ACC TTG GAC ATG GAA GAC TGT GGC TAC AAC ATT
 422 Val His Asp Glu Phe Arg Thr Ala Ala Val Glu Gly Pro Phe Val Thr Leu Asp Met Glu Asp Cys Gly Tyr Asn Ile

3016 CCA CAG ACA GAT GAG TCA ACC CTC ATG ACC ATA GGC TAT GTC ATG GCT GGC ATC TCC GGC CTC TTC ATG CTG CCA CTC
 448 Pro Gln Thr Asp Glu Ser Thr Leu Met Thr Ile Ala Tyr Val Met Ala Ala Ile Cys Ala Leu Phe Met Leu Pro Leu

3094 TGC CTC ATG GTG TGT CAG TGG GGC TGC CTC GGC TGC CTG GGC CAG CAG CAT GAT GAC TTT GCT GAT GAC ATC TCC CTG
 474 Cys Leu Met Val Cys Gln Trp Arg Cys Leu Arg Cys Leu Arg Gln Gln His Asp Phe Ala Asp Asp Ile Ser Leu

3172 CTG AAG TGA GGAGGCCCATGGGCAGAAGATAGAGATTCCOCTGGACCACACCTCCGTTGTTCACTTTGGTCACAAGTAGGAGACACAGATGGCACTGTGGCC
 500 Leu Lys ...

3275 AGAGCAOCTCAGGACCOCTCCOCCACCCACCAATGCTCTGCTTGTATGGAGAAGGAAAAGGCTGGCAAGGTGGGTTCAGGGACTGTACCTGTAGGAAACAGAAAA

3381 GAGAAGAAAGAAGCACTCTGCTGGGGGAATACTCTTGGTCACCTCAAATTTAAGTGGGAAATTTCTGCTGCTTGAAACTTCAGCCCTGAACCTTTGTCCACCATT

3487 CCTTTAAATTTCTCCAACCCAAAGTATTCTCTTTCTTTAGTTTCAGAACTACTGGCATCACACGAGTTACCTTGGGGTGTGTCCTGTGGTACCTTGGCAGAGA

HindIII

3593 AGAGACCAAGCTTGTTCCTCTGCTGGCCAAAGTCAGTAGGAGAGGATGCACAGTTTGCTATTGTCTTTAGAGACAGGGACTGTATAACAAGCCTAACATTGGTGC

3699 AAAGATTGCTCTTGAATTAATAAAAAAAAACTAGATTGACTATTTATACAAATGGGGGGGCTGGAAAGAGGAGAAGGAGAGGGAGTACAAAGACAGGGAATAGTG

3805 GGATCAAAGCTAGGAAAGGCAGAAACACAACCACTCAOCCAGTCTAGTTTATAGACCTCATCTCCAAGATAGCATCCCATCTCAGAAGATGGGTGTGTTTCAATG

3911 TTTTCTTTTCTGTGGTTGCAGCCTGAOCCAAAGTGAGATGGGAAGGGCTTATCTAGCCAAAGAGCTCTTTTATAGCTCTCTTAAATGAAGTGCCCACTAAGAAGTT

4017 CCACTTAACACATGAATTTCTGCCATATTAATTTTCATGTCTCTATCTGAACCAOCCCTTATTTCTACATATGATAGGCAGCACTGAAATATCTTAACCCCTAAGC

4123 TCCAGGTGCCCTGTGGAGAGCAACTGGACTATAGCAGGGCTGGGCTCTGTCTTCTGGTTCATAGGCTCACTCTTTCCCCCAAATCTTCTCTGGAGCTTTGCAGC

4229 CAAGGTCTAAAAGGAATAGGTAGGAGAOCTCTTCTATCTAATCTTAAAGCATAATGTTGAACATTCACTCAACAGCTGATGCCCTATAACCCCTGCCCTGGATT

4335 TCTTCTATTAGGCTATAAGAAGTAGCAAGATCTTTACATAATTCAGAGTGGTTTCATGTGCTTCTTACCCCTCTCTAATGGCCCCCTCCATTTATTTGACTAAAGCA

4441 TCACACAGTGGCACTAGCATTATACCAAGAGTATGAGAAATACAGTGCTTTATGGCTCTAACATTACTGCTTCAGTATCAAGGCTGCTGGAGAAAGGATGGCAG

4547 CCTCAGGCTTCTTATGTCTCCACCACAAGAGCTOCTTGATGAAGGTCACTCTTTTCCCTATCTGTCTTCCCTCCCGCTCTAATGGTAAGTGGGTACC

4653 CAGGCTGGTTCTTGGCTAGGTAGTGGGAACCAAGTTTCAATTAOCTCCCTATCAGTTCTAGCATAGTAAACTACGGTACAGTGTAGTGGGAAGAGCTGGGTTTTC

4759 CTAGTATACCACTGCATCTACTCTACCTGGTCAOCCCGCTGCTTCCAGGTATGGGACCTGCTAAGTGTGGAATTACCTGATAAGGGAGAGGGAAATACAAGGA

4865 GGGCTCTGGTGTCTCTGGCTCAGCCAGCTGCCACAAGCCATAAACCAATAAACAAGAATACTGAGTCAGTTTATCTGGGTCTCTTTCATTCCTCACTGCA

4971 CTGTGTGCTGCTTTGGCTGACTGGGAACACCCATAACTACAGAGTCTGACAGGAAGACTGGAGACTGTCCACTTCTAGCTGGAACTTACTGTGTAATAAATCTT

5077 TCAGAACTGCTACCATGAAGTGAAAAATGOCACATTTTGCTTTATAATTTCTACCATGTTGGGAAAAACTGGCTTTTCCAGCCCTTCCAGGGCATAAACTCA

5183 ACCCCTTGATAGCAAGTCCCATCAGCCTATTATTTTAAAGAAAACCTTGCACTGTGTTTCTTTTACAGTTACTTCTTCTGCCCCAAAATTATAAACTCT

FIG. 13C

[illegible]

FIG. 13D

FIG. 13E

15041 CTGGCAAACTGTGATGGACGACACCGTCAGTGGTCCGTGGCGCAGGCTCTCGATGAGCTGATGCTTTGGGCGCAGGACTGCCCGGAAGTCCGGCACTGTGCAC
 15147 GCGGATTTCGGCTOCAACAATGTCTGACGGACAATGGCCGCATAACAGCGGTCAATTGACTGGAGCGAGGGGATGTTGGGGGATTCCCAATAOGAGGTGGCAACA
 15253 TCTTCTTCTGGAGGCGGTGGTTGGCGGGTATGGAGCAGCAGACGGCTACTTGGAGCGGAGGCATCCGGAGCTTGCAGGATCGCCGGGCTCCGGGGGTATATGCT
 15359 CCGCATTTGGTCTTGACCAACTCTATCAGAGCTTGGTTGACGGCAATTTGGATGATGCAGCTTGGGCGCAGGGTGGATGGCAAGCAATGGTCCGATCCGGAGCCGGG
 15465 ACTGTGGGGGTACACAAATGCCCGCAGAAGCGCGCGCTCTGGACCGATGGCTGTGTAGAAGTACTGGCGATAGTGGAAACGGGAGATGGGGGAGGCTAACTG
 15571 AAACAAGGAGAGACAATACCGGAAGGAACCGCGCTATGACGGCAATAAAAGACAGAATAAAACGCAAGGGTGTGGGTGTTTGTTCATAAACCGGGGTTTC
 15677 GGTCCAGGGCTGGCACTCTGTGATACCCACCGAGACCCCATTTGGGGCCAATACGCCCGGTTTCTTCTTTTCCCAACCCACCCCAAGTTGGGGTGAAGG
 15783 OCGAGGGCTGGCAGCAACGTGGGGCGGCAGGCCCTGCCATAGCCACTGGCCCGTGGGTTAGGGAAGGGGTCCCCCATGGGGAATGGTTTATGGTTGGTGGGGG
 15889 TTATTATTTGGGCGTTGGGTGGGGTCTGGTCAAGACTGGACTGAGCAGACAGACCATGGTTTTTGGATGGCTGGGCATGGACCGCATGTACTGGCGGACAC
 15995 GAACACCGGGCGTCTGTGGCTGCCAAACACCCCGACCCCAAAAAACACCGCGCGGATTTCTGGGTGCCAAGCTAGTCGACCAA

Sall



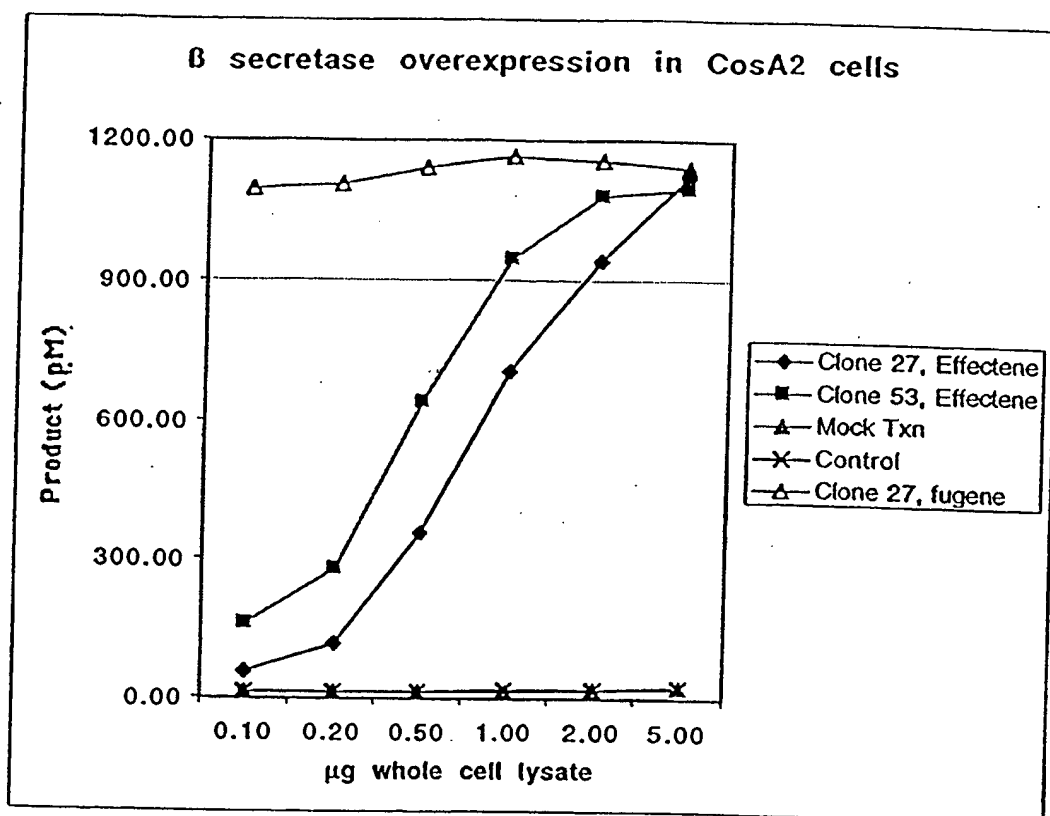


FIG. 14

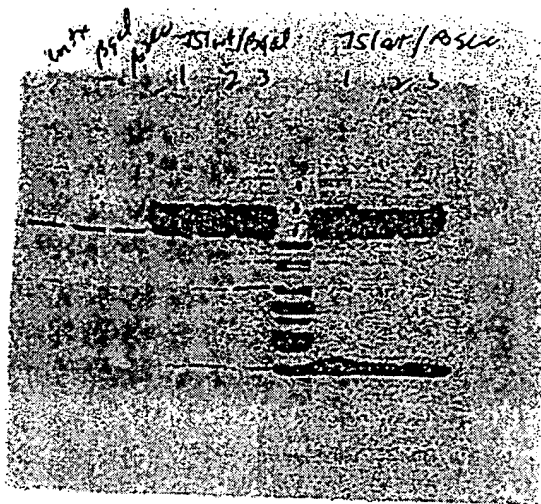


FIG. 15A

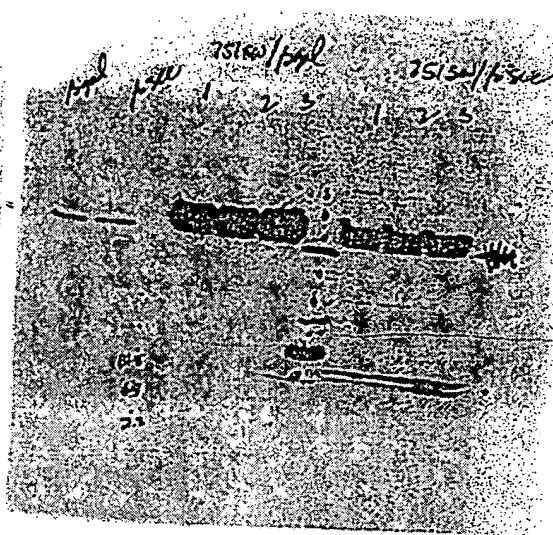


FIG. 15B

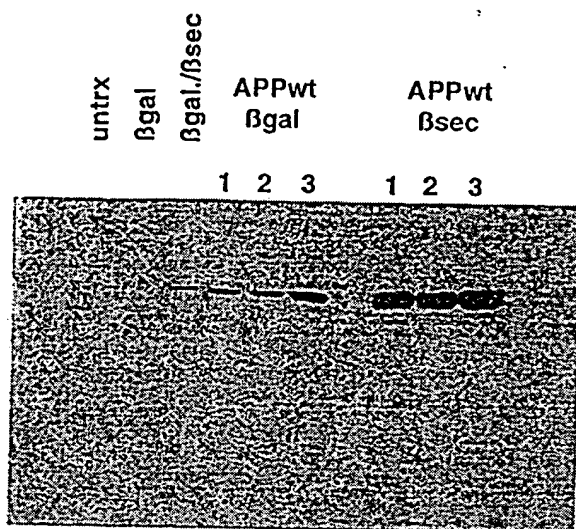


FIG. 16A

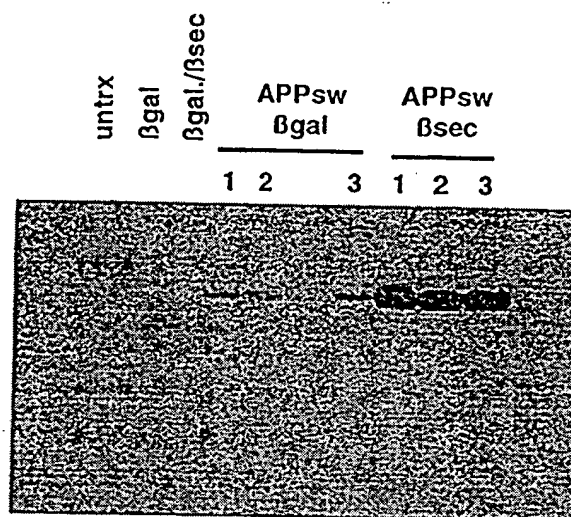


FIG. 16B

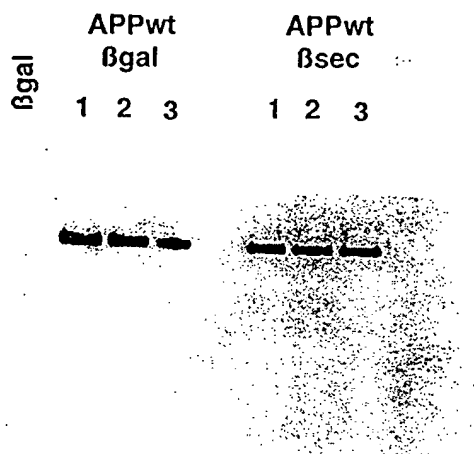


FIG. 17A

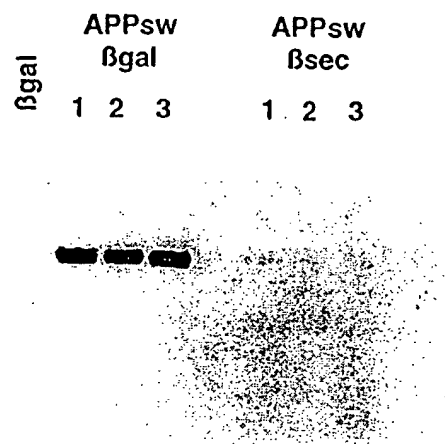


FIG. 17B

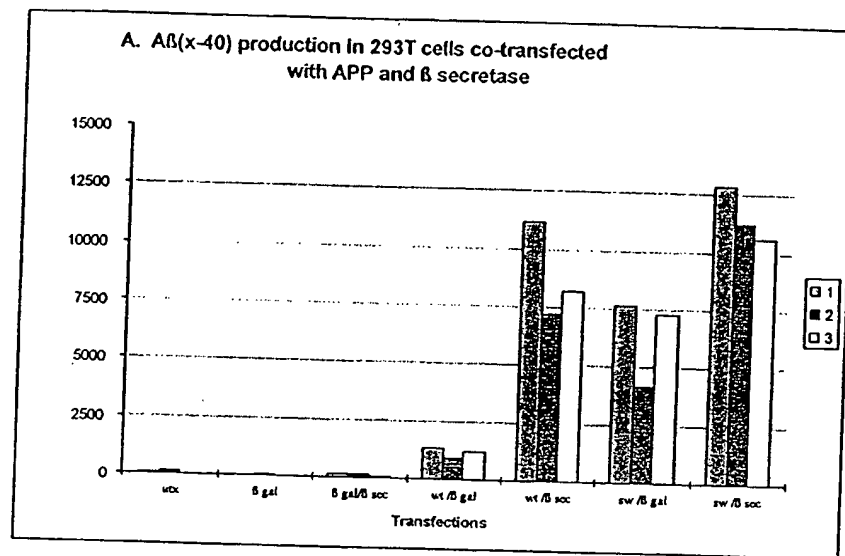


FIG. 18

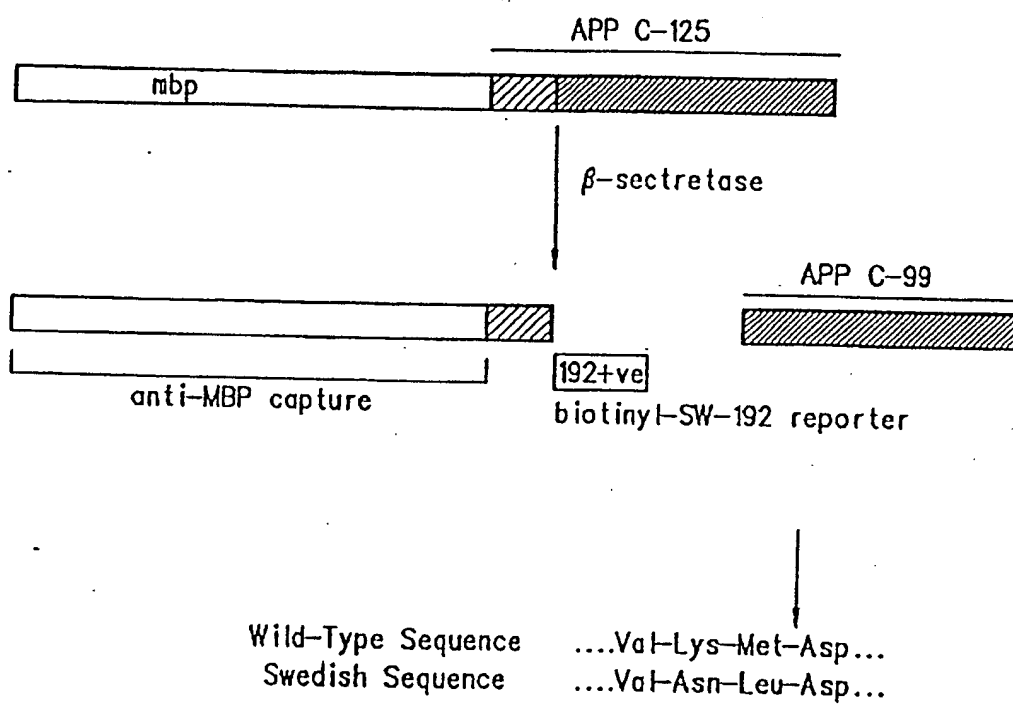


FIG. 19

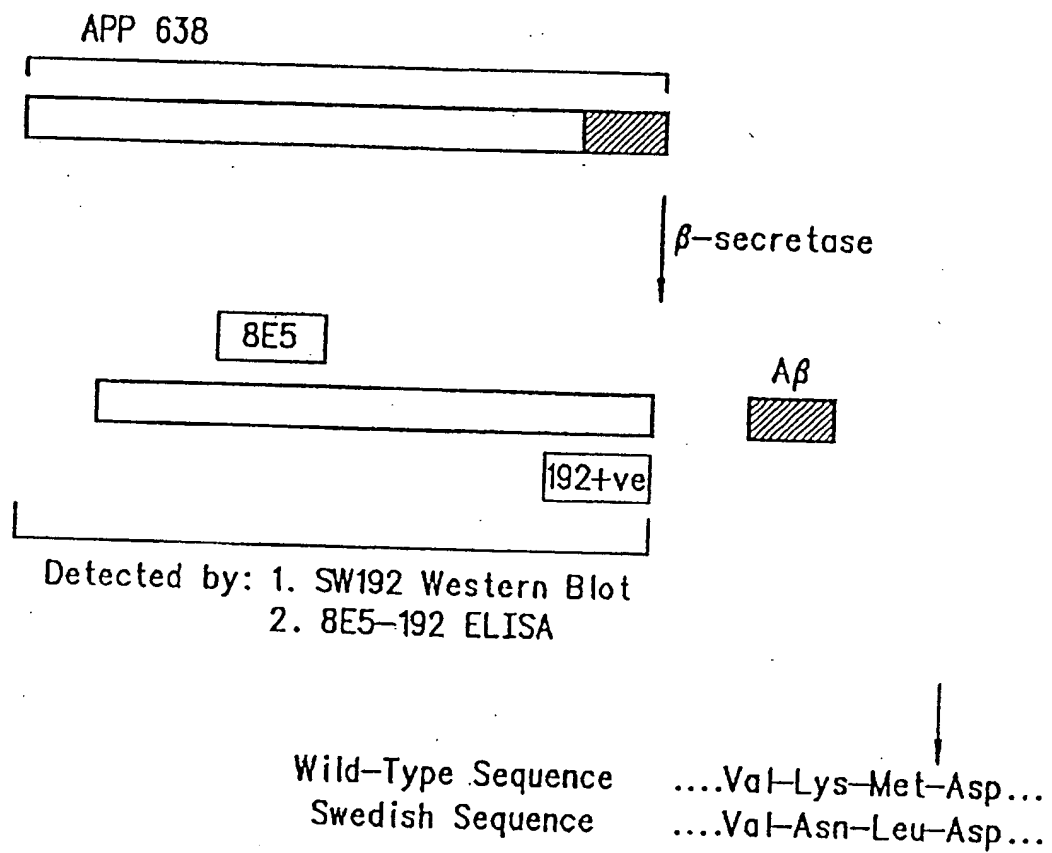


FIG. 20

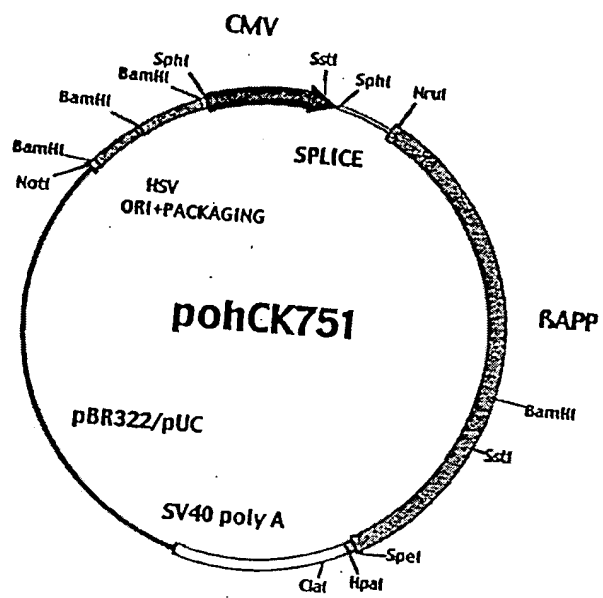


FIG. 21